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Abdominal involvement as a primary manifestation of systemic or isolated gastrointestinal vasculitis

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Abstract

Systemic vasculitides can cause a wide variety of gastrointestinal manifestations (GI) ranging from mild and frequently nonspecific abdominal pains to potentially life-threatening bowel perforations. Vascular involvement in systemic vasculitides can affect any GI blood vessel, most commonly mesenteric, hepatic, or splenic arteries. Inflammatory changes affecting different layers of arterial vessel walls can lead to aneurysmatic dilatation or blood vessel occlusion with subsequent organ ischemia leading to mucosal ulcerations, GI bleeding, perforations, or bowel obstruction. While the presence of extraintestinal manifestations may aid in diagnosis, delays in making appropriate diagnoses and rapid initiation of glucocorticoid and immunosuppressive treatment can have detrimental consequences. Awareness of isolated gastrointestinal vasculitis is of particular importance as it frequently remains undiagnosed until end-stage organ damage becomes apparent. Vasculitis mimics such as vascular Ehlers-Danlos syndrome or fibromuscular dysplasia add another lay of complexity in approaching patients with suspected GI vasculitis and should always be carefully considered.

Keywords: Vasculitis, abdominal symptoms, Isolated gastrointestinal vasculitis, vasculitis mimics

INTRODUCTION

Vasculitides represent a group of systemic diseases characterized by inflammation of blood vessel walls. They are categorized as different clinical entities based on the size of the involved arterial vessel, and

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additional consensus criteria reflecting different patterns of systemic involvement[1]. In a more recent classification of vasculitides, localized vasculitis (single-organ vasculitis) including localized vasculitis of the GI tract (LVGT) has been included[1-4]. In this article, we discuss clinical manifestations in patients presenting with LVGT and compare them to patterns of gastrointestinal organ involvement in patients with different forms of systemic vasculitis. We also discuss vasculitis mimics (e.g., vascular Ehlers-Danlos syndrome (EDS); fibromuscular dysplasia (FMD), *etc.*), which at times may cause very similar clinical manifestations that can be difficult to distinguish from vasculitides. Table 1 gives an overview of systemic vasculitis and vasculitis mimics that can present with abdominal manifestations.

SINGLE-ORGAN VASCULITIS: LOCALIZED VASCULITIS OF THE GASTROINTESTINAL TRACT

Vasculitis involving the GI tract is more commonly secondary to underlying systemic inflammatory diseases such as Polyarteritis nodosa (PAN), ANCA-associated vasculitis (AAV), and Henoch-Schoenlein purpura (HSP). Less commonly, GI vasculitis can occur as a primary disease in isolation, i.e., localized vasculitis of the gastrointestinal tract (LVGT)[5]. The incidence of LVGT is very low and is rarely considered as a differential in patients presenting with isolated abdominal symptoms. However, missing these cases may be detrimental to the patient. Once a diagnosis of LVGT is considered, it requires a comprehensive approach to identify underlying primary etiology and, in many instances, a multidisciplinary approach between the vascular surgeon, GI specialist, and rheumatologist, just to name a few.

Suspicion of a LVGT should be raised in patients with refractory GI involvement who are unresponsive to traditional therapeutic approaches, in patients with a known history of autoimmune disorders such as systemic lupus erythematosus or systemic vasculitis, and in those with evidence of (additional) unexplained constitutional or multisystemic symptoms. Even when one suspects a LVGT, a diagnosis is extremely difficult to make. No specific laboratory tests are available apart from anti-neutrophil cytoplasmic antibody testing (ANCA) which are only positive in a minor subset of patients with LVGT. Diagnosis of LVGT depends on high clinical acuity supported by imaging studies and biopsy results. Interpretation of imaging results may itself be difficult and highly subjective. Another layer of concern comes from the frequently encountered inaccessibility of appropriate tissue for biopsy. Furthermore, biopsies themselves can be inconclusive, for example, superficial mucosal biopsies provide a very low yield.

Clinical features and outcomes of patients with LVGT have been described in small case series. By analyzing records from the Armed Forces Institute, Burke *et al.* were able to identify 63 patients diagnosed with this condition between 1970 and 1992[6]. Although all these patients had pathologic evidence of vasculitis, some of them did have comorbidities such as rheumatoid arthritis or systemic lupus erythematosus, which are known to cause GI vasculitis in some instances. Longitudinal follow-up showed that 6 of these patients with LVGT progressed to full-blown systemic vasculitis, thus signifying the importance of a long follow-up and emphasizing that LVGT patients are at risk of transitioning into systemic vasculitis over time. Salvarani *et al.* identified 18 patients with LVGT diagnosed over a 12-year period[5]. Only patients with typical angiographic findings of vasculitis and histopathologic results were included, while those with associated autoimmune diseases or evidence of multi-organ systemic vasculitis were excluded. These 18 patients showed a variety of clinical manifestations including a history of GI bleeding with evidence of gastric, duodenal or jejunal ulcerations, ischemic colitis, bowel obstruction, or bowel infarctions. The most common presenting symptom was abdominal pain in 17 out of 18 patients. Twelve of these patients presented with acute abdomen requiring urgent surgical intervention, most commonly due to acute cholecystitis or gallbladder infarction. Patients who did not present with abdominal pain usually presented with acute GI bleed. Imaging studies were consistent with arterial involvement. Stenosis was the most

Table 1. Clinical characteristics of vasculitides and mimics

Vasculitides and mimics	Vessel size involved	Common clinical manifestations	GI manifestation	Features on imaging
ANCA vasculitis (GPA)	Small vessel	ENT involvement, pulmonary nodules, hemoptysis, purpura, mononeuritis multiplex, renal disease	Poor prognostic sign. Nonspecific symptoms: severe GI bleeding, ulcers, bowel infarctions, bowel perforations	Imaging of the bowels is nonspecific, with findings of bowel wall thickening, dilation of bowel segments, and bowel perforation. GPA can mimic IBD
Polyarteritis nodosa (PAN)	Medium vessel	Palpable purpura, livedo reticularis, mononeuritis multiplex, testicular pain, abdominal pain, hypertension	Postprandial pain, organ infarctions, bowel perforations. cholecystitis, pancreatitis, appendicitis	Angiography is a primary modality. Stenotic changes, occlusions, and aneurysms tend to be multiple and are particularly seen along the renal and hepatic arteries
DADA 2	Medium vessel	Typical childhood onset, resembles PAN, associated with more CNS manifestations and bone marrow failure	Resembles PAN	Like PAN
Takayasu arteritis	Large vessel	Pulseless disease, onset < 40 years, intermittent claudication, arterial bruits, decreased pulse and asymmetric blood pressure	Abdominal pain, abdominal bruits, symptoms of mesenteric ischemia, cases resembling ulcerative colitis	CTA and MRI can show luminal occlusion, mural thickening, aneurysm formation, and thrombosis. PET-CT & PET-MRI can distinguish between active and inactive lesions
Giant cell arteritis	Large vessel	Onset > 50 years of age, headaches, scalp tenderness, jaw claudication, polymyalgia rheumatica, and visual disturbances	Asymptomatic liver enzyme elevations, bowel Ischemia, granulomatosis hepatitis	Similar findings as Takayasu. Angiography is most helpful. All patients should be screened to rule out abdominal aortic aneurysm at diagnosis and every 5 years
IgA vasculitis	Small vessel	Palpable purpura, arthritis, abdominal pain, and renal disease	Bowel wall edema, necrosis, perforations, intussusception	CT scan can show bowel wall edema, necrosis, perforations, or intussusception
Cryoglobulinemic vasculitis	Small vessel	Cutaneous lesions, sensorimotor polyneuropathy, arthralgias, and renal involvement	Mesenteric vasculitis, duodenal involvement, pancreatitis, chronic liver disease	Imaging is nonspecific and can range from mesenteric ischemia to pancreatitis and chronic liver disease on conventional CT imaging
Behcet's	Variable vessel	Recurrent oral and genital ulcerations, large vein and arterial thrombosis, eye lesions, erythema nodosum - like lesions, positive pathergy test	Mimics Crohn's disease with ileocecal involvement, intestinal ischemia, and infarction	Angiography: arterial & venous thrombosis, pseudoaneurysms. CT findings: bowel perforation, fistula formation, intestinal obstruction, or abdominal mass
Fibromuscular dysplasia	Variable arterial involvement	Depends on the arterial segment involved. Intermittent claudication, postprandial abdominal pain, weight loss, arterial bruit, hypertension	Mimics chronic mesenteric ischemia with complaints of postprandial abdominal pain. Lack of fever, rash, *etc.*	Arteriography remains the gold standard and can detect pressure gradients across stenosis
Median arcuate ligament syndrome	Celiac artery compression	Primarily GI manifestations. Weight loss resulting from abdominal pain	Postprandial abdominal pain, lack of constitutional symptoms such as fever or rash	CTA, MRA and duplex abdominal ultrasound during inspiration and deep expiration to identify active arterial compression. Can be an incidental finding
Vascular EDS	Medium & large artery	Subtle clinical findings. Translucent skin, easy bruising, varicosities at a young age. Micrognathia, narrow nose, ear changes	Acute abdominal pain, infarcts (kidney or spleen), spontaneous rupture	CTA or MRI can show arterial dissections, aneurysms, and ruptures

ANCA: Anti-neutrophil cytoplasmic antibodies; CT: computed tomography; CTA: computed tomography angiography; DADA 2: deficiency of adenosine deaminase 2; ENT: ear nose and throat; GI: gastrointestinal; GPA: granulomatosis with polyangiitis; IBD: inflammatory bowel disease; PAN: polyarteritis nodosa; PET-CT: positron emission tomography- computed tomography, PET-MRI: positron emission tomography-magnetic resonance imaging; MRA: magnetic resonance angiogram; Vascular EDS: vascular Ehlers-Danlos syndrome.

common lesion, followed by dilation, aneurysm, obstruction, and arterial wall thickening. Superior mesenteric arteries, followed by celiac and hepatic arteries, were primarily affected. Splenic, hepatic, and intestinal infarcts were observed in a few cases.

Treatments and outcomes were variable. Those with localized vasculitis of the gallbladder, pancreas, or appendix showed excellent prognosis with just a surgical intervention. Hernandez-Rodrigues *et al.* also concluded that single-organ vasculitis involving the gallbladder did not require therapy beyond surgical removal and have an excellent prognosis[7]. However, those with intestinal involvement had much less favorable outcomes, frequently requiring immunosuppressive therapy.

GASTROINTESTINAL INVOLVEMENT IN PRIMARY SYSTEMIC VASCULITIDES

Based on the caliber of arterial vessel, primary systemic vasculitides can be categorized as those affecting primarily small vessels, namely IgA vasculitis, cryoglobulinemic vasculitis, and AAV; medium-size vessels, such as PAN; and those affecting large vessels, i.e., Takayasu arteritis (TAK) and Giant cell arteritis (GCA). Behcet's syndrome can affect blood vessels of variable sizes and types. GI involvement, when present in these conditions, is an indicator of disease severity[8]. Secondary vasculitides, as the term implies, are defined as secondary manifestations of systemic diseases such as systemic lupus erythematosus or rheumatoid arthritis. Cases that neither fit into the category of either primary or secondary vasculitides as discussed above are now classified as "single-organ vasculitis" (LVGT). When approaching patients with suspected LVGT, vasculitis "mimickers" should also be considered and are discussed below.

ANCA-ASSOCIATED VASCULITIS

Gastrointestinal involvement is not considered to be a common phenomenon in ANCA-associated vasculitis (AAV). However, when present, it may cause serious morbidity and high mortality. AAV is categorized as a small vessel vasculitis but may sometimes also affect medium-sized vessels[9,10]. The AAV can be subdivided into granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA). Each category of AAV is a multisystemic vasculitis with its own predilection for organ involvement. Typical features of GPA include upper and lower respiratory tract and renal involvement. Patients may also present with neurologic involvement, and skin manifestations such as palpable purpura. Patients with MPA typically present with more aggressive renal disease but lack cartilage involvement and granulomatous inflammation typically seen in GPA[11]. Patients with EGPA present with a history of asthma, nasal polyposis, and peripheral blood eosinophilia. Laboratory investigations are of high importance and should include testing for inflammatory markers. Kidney function tests should go beyond the determination of the serum creatinine level and should include quantification of the urine protein loss and urine microscopy testing for the presence of typical red cell casts. Serologic testing with determination of ANCA titers and ANCA subtypes (cANCA *vs.* pANCA *vs.* atypical pANCA) is also of utmost importance and may aid in diagnosis.

Regardless of the AAV subtype, GI involvement in AAV is rarely the initial or primary feature of systemic vasculitis. Like other forms of vasculitis, AAV can cause a wide range of GI manifestations secondary to ischemic changes. Those include severe GI bleeding, bowel infarctions with subsequent bowel perforations, and ulcerations along the GI tract resembling those seen in inflammatory bowel diseases (IBD). At times, AAV may present with conditions such as pancreatitis, cholecystitis, or hepatitis. Cabral *et al.* noticed that GI manifestations were more common in patients with MPA compared to GPA[12]. Due to their relative rarity and multitude of clinical manifestations, atypical GI involvement frequently causes delays in diagnosis and poses a diagnostic challenge. The clue to diagnosis lies in clinicians' awareness of the multisystemic disease character of AAV; therefore, the value of comprehensive history-taking and detailed physical examination should not be underestimated. Imaging studies, although in general helpful in most patients with abdominal pathology, may not be conclusive in patients with AAV, especially those with the GPA. Imaging of the bowels is frequently nonspecific, with findings of bowel wall thickening, dilation of bowel segments, and even evidence of bowel perforation. Clinically, GPA, with its known ability to cause

granulomatosis inflammation, can mimic not only inflammatory bowel diseases such as Crohn's disease but also infectious diseases such as tuberculosis[13].

Treatment of AAV consists of trials of glucocorticoids, steroid-sparing agents such as C5a inhibitors (e.g., Avacopan)[14] and immunosuppressive therapy dependent on the type and severity of underlying disease. Induction therapy frequently involves the use of Cyclophosphamide, Rituximab or Mepolizumab, while the maintenance therapy is primarily centered around the use of Rituximab (anti-CD20), or, alternatively, oral agents such as Azathioprine or Methotrexate[15].

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis first described in 1866 by Adolf Kussmaul and Rudolph Maier. PAN typically affects medium-sized arteries and is not associated with positive ANCA testing. It may present as an idiopathic primary form, or less frequently, it may be secondary to hepatitis B infection, systemic rheumatic diseases, auto-inflammatory diseases, and malignancies such as hairy cell leukemia[16].

PAN, by definition, is a necrotizing focal and segmental vasculitis due to the deposition of circulating immune complexes causing edema, inflammation, and vessel wall necrosis[17,18]. Persistent inflammation consequently leads to vessel lumen narrowing and thrombosis, with subsequent ischemia and infarction[19]. Affected vessel walls may also weaken from inflammation leading to aneurysmal development. PAN affects multiple organ systems, of which the kidney is the most affected, with patients typically presenting with hypertension[20]. PAN is one of the vasculitides wherein gastrointestinal involvement is frequent, with estimates ranging from 14% to 65% of patients[21,22]. Patients may also report symptoms of neurologic involvement, e.g., mononeuritis multiplex or polyneuritis[23]. Skin lesions resembling erythema nodosum, livedo reticularis, and lower extremity ulcerations are often helpful clues that GI manifestations may be caused by a systemic disease such as PAN. Physicians should also be aware of associated constitutional symptoms such as fever, weight loss, fatigue, and arthralgia.

When the GI tract is involved, abdominal pain is often present and severe[21]. Abdominal pain is often described as a postprandial pain and the term "intestinal angina" is frequently used[24]. When inflammation targets the GI tract, the small bowel and gallbladder are the two primary sites that are most affected[6]. Ischemia limited to mucosal or submucosal tissue may lead to ulcerations and GI bleeding[25]. When transmural ischemia develops, then perforations, bowel wall necrosis, and infarction can be anticipated[26]. In these instances, colonoscopies carry a much higher risk of perforations[21]. Early diagnosis and management are essential to minimize the significant mortality risk associated with bowel perforation. Other causes of acute abdomen in PAN include cholecystitis, gallbladder infarction, appendicitis, and pancreatitis.

Clues to diagnosing PAN include the presence of multiple vessel lesions, along with refractory/progressive pathologic features such as ischemic pseudo-membranous colitis, or gastric, duodenal and jejunal ulcers. Pancreatic involvement may range from acute pancreatitis to pancreatic infarcts and even evidence of pancreatic insufficiency[27-29]. Hepatobiliary tract involvement has also been well described. In cases where the necrotizing vasculitis affects either the portal vein or hepatic artery, this can lead to liver infarction, acute liver failure, or nodular regenerative hyperplasia[30-32]. Acalculous gangrenous cholecystitis may be due to arteritis involving the gallbladder wall[33], while intrahepatic sclerosing cholangitis may occur secondary to vasculitis affecting the blood vessels supplying small bile ducts[32].

Angiography is a primary modality to confirm the diagnosis of PAN. Stenotic changes, occlusions, and aneurysms tend to be multiple and are particularly seen along the renal and hepatic arteries[21].

Without aggressive immunosuppressive treatment, patients with PAN generally have a poor prognosis[34]. As already mentioned above, Gi tract involvement is a poor prognostic factor[35]. Corticosteroids combined with immunosuppressive therapy, such as cyclophosphamide, have been shown to reduce the incidence of relapses in PAN[36].

VASCULITIS SECONDARY TO DEFICIENCY OF ADENOSINE DEAMINASE 2

A newly recognized auto-inflammatory disease, named deficiency of adenosine deaminase 2 (DADA 2), is secondary to mutations in adenosine deaminase 2 gene (ADA2)[37,38]. Better awareness of this condition led to increased recognition of this PAN mimicker (approximately 1 in 222,000)[39]. DADA 2 is recessively inherited with incomplete penetrance[40]. Multiple pathogenic variants have been described. Patients with homozygous G47R mutations typically exhibit the vasculitis phenotype that resembles the PAN. Other described variants are associated with severe hematologic compromise and bone marrow failure[41].

Most patients exhibit first disease manifestations in childhood, typically between ages 5-7 years. Approximately 25% of patients are diagnosed before the age 1 and 77% by age 10[42,43]. With growing awareness of this condition, new cases are also recognized within the adult population.

Vasculitic DADA 2 syndrome is similar clinically to classic PAN[37,38] and presents as a multisystemic disease with features of systemic inflammation, i.e., elevated inflammatory markers and transaminase levels, fevers, lymphadenopathy, hepatosplenomegaly, skin manifestations (such as livedo racemose, skin necrosis, and subcutaneous nodules). CNS and PNS involvement are also common, resulting in recurrent strokes, cranial and peripheral neuropathies, uveitis, optic nerve damage, and neurosensory hearing loss. GI involvement has been reported, although less common than central nervous system involvement. GI manifestations include bowel infarctions, pancreatitis, and GI bleeding with underlying pathology highly resembling PAN. DADA2 should be considered in younger patients with suspected GI vasculitis, especially if the patient has a positive family[37,38].

Depending on a genetic variant of DADA 2, bone marrow failure may be seen with features of anemia, neutropenia, and lymphopenia and associated immunodeficiency with low IgM, IgA, and IgG levels, resembling common variable immunodeficiency. Measurement of ADA2 enzymatic activity in serum or plasma can help diagnose DADA2. Once DADA 2 is diagnosed, recommended treatment options for the vasculitis phenotype include the use of TNF-α inhibitors (either etanercept, adalimumab, infliximab, or golimumab)[44,45]. TNF-α has a proven role in driving systemic inflammation and vasculitis in DADA2 patients, as reflected by the efficacy of TNF-α inhibitors in preventing the recurrence of strokes[43]. In a recent case series published by Ombrello *et al.*, 15 patients with a history of strokes secondary to DADA 2 were successfully treated with either etanercept, adalimumab, infliximab, or golimumab. No recurrence of strokes was observed in patients after initiation of anti-TNF-α treatment compared to frequent episodes of strokes prior to initiation of this treatment[45].

In summary, patients who present with GI vasculitis with clinical features mimicking PAN, with or without an associated hypogammaglobinemia or cytopenia, should always be evaluated for possible DADA 2 syndrome.

TAKAYASU ARTERITIS

Takayasu arteritis (TAK), also known as a "pulseless disease", is a chronic large vessel vasculitis of unknown etiology primarily affecting aorta and its branches (ACR). TAK is more prevalent in young women, primarily of Asian and Latin American descent[46]. Vascular inflammation leads to arterial stenosis, occlusion, or dilatation of blood vessels[47]. Narrowing of the blood vessel lumen, in turn, reduces the blood flow in affected organs, resulting in ischemia and subsequent infarction. TAK is characterized histologically by inflammation affecting all layers of the arterial wall, including distraction of the medial smooth muscles and elastic layers, cellular infiltration and collagenous fibrosis in the media, intimal fibrosis, thickening, and atheromatous lesions collectively known as "pan-arteritis"[48].

Clinical manifestations may differ depending on a geographic region. In Japan, patients tend to have more ischemic manifestations due to cervical vessel involvement, such as dizziness, syncope, differences in systolic blood pressure between arms, and visual disturbances[48]. Moriwaki *et al.* found that Japanese patients had more aggressive disease and more prolonged course compared to patients in India[49]. Goel *et al.* performed cluster analysis based on a pattern of arterial involvement in different regions of the world. Studies showed that North Americans tended to have more common involvement of the left carotid and subclavian arteries while the Indian population had more common renal involvement[50].

Gastrointestinal involvement in TAK is relatively rare. Schmidt *et al.*, by analyzing 126 patients with documented TAK, calculated that 16% of patients complained of abdominal pain, 14% had abdominal bruits, and 4% had evidence of mesenteric ischemia[51]. Other studies even suggested that ulcerative colitis may be a major complication of TAK[52]. Sy *et al.* evaluated patients with TAK and found that 5% of them also carried a diagnosis of inflammatory bowel disease[53]. HLA-B*52:01 gene was shared between the TAK and ulcerative colitis, suggesting a possible overlap[53].

Diagnosis of TAK is based on typical clinical features and is supported by imaging studies. PET-CT has a unique place in the diagnosis of TAK. It provides information on both metabolic and anatomical status of blood vessels, which aids not only in confirming the diagnosis, but also allows better monitoring of the treatment and may predict possible future relapses. PET-MRI provides a similar advantage but with the extra benefit of lower radiation exposure compared to PET-CT and hence can be used for follow-up scans in younger individuals[54]. CT angiographies (CTA) are readily available, but their benefit is limited by high radiation exposure. As TAK is known to cause frequent relapses, the choice of imaging modality, including its ability to differentiate between active inflammation and chronic fibrotic changes, is of crucial importance. CTA can identify anatomical abnormalities such as luminal occlusion, mural thickening, aneurysm formation, and thrombosis but is limited in its ability to differentiate between active and inactive diseases. EULAR, therefore, recommended MRI as a first-line imaging option for suspected TAK patients. It provides high-resolution imaging and low radiation exposure. Post contrast enhancement is believed to reflect ongoing inflammation and may also help identify associated cardiac involvement[55]. The goal of treatment is to limit the progression of the disease and allow revascularization. Vascular intervention, if necessary, should ideally be performed during periods of remission. Saadoun *et al.* noticed that the likelihood of complication was 7 times higher when the procedure was done in the presence of active inflammation[56].

Corticosteroids remain the mainstay of treatment of TAK. Different geographic regions reported success by using a variety of different DMARDs and biologics. Methotrexate, leflunomide, and mycophenolate mofetil were a few DMARDs which gained popularity. Tocilizumab, an anti-IL-6 inhibitor, and TNF-a inhibitors have also been studied and are frequently used for management. A multicenter retrospective cohort study

showed similar remission rates, relapses, and mortality when TNF-a inhibitors and tocilizumab were compared[57]. However, despite initial treatment success, relapses are common and disease-associated morbidity remains high. Identifying active ongoing inflammation remains a challenge as TAK lacks reliable biomarkers[58] and is highly dependent on clinical assessment. The role of imaging remains an active area of ongoing research and the development of multimodal scoring assessments that correlate well with disease remission and can predict disease relapse continue to be topics of high scientific interest.

GIANT CELL ARTERITIS

Giant cell arteritis (GCA) is another form of large vessel vasculitis known to affect the aorta and great vessels with a predilection for carotid and vertebral arteries[1]. GCA is the most common form of systemic vasculitis in elderly patients[59]. GCA incidence increases with age, being almost 10 times more common among patients in their 80s compared to patients in their 50s. GCA is more commonly reported in patients of north European descent. The typical presentation of GCA includes headaches, jaw claudications, polymyalgia rheumatica-like symptoms, fevers, and visual disturbances[60]. Gastrointestinal involvement associated with GCA is rare and considered to be an atypical disease manifestation. Involvement of the abdominal aorta with GCA can cause abdominal pain. The median time between a diagnosis of GCA and the development of abdominal aortic aneurysm/dissection is 6 to 7 years[61]. It is recommended that all patients with GCA should be screened for an abdominal aortic aneurysm at diagnosis and followed every 5 years[62]. A multitude of studies have shown that up to one-third of patients with GCA may have asymptomatic liver enzyme abnormalities, especially elevation of alkaline phosphatase and GGT[63]. Mesenteric vessels are rarely affected in GCA, but when it occurs, it may lead to bowel ischemia[64]. Hepatic artery vasculitis[65] and coexisting granulomatosis hepatitis have been observed in some studies[66]. As GI involvement is not a common manifestation in GCA, we anticipate a difficulty in making this diagnosis. The presence of persistent fever, myalgias, associated symptoms of headaches or visual disturbances, elevated inflammatory markers (ESR or CRP), and elevated liver abnormalities (ALP and GGT) should suggest a further work-up to evaluate for possible GCA vasculitis. Glucocorticoids continue to be the cornerstone of therapy for GCA, often with adjunctive biologics such as tocilizumab. Based on randomized clinical trial data obtained from the GIACTA trial, tocilizumab is now considered a first-line steroid-sparing treatment with relatively good efficacy and tolerability[67]. Endovascular procedures or surgery should be considered when appropriate.

IGA VASCULITIS

IgA vasculitis, formerly known as Henoch-Schoenlein purpura, is a small vessel vasculitis caused by perivascular deposition of IgA1 containing immune complexes. IgA vasculitis can occur as a single organ-limited vasculitis, i.e., presenting as a skin disease or alternatively as a systemic disease[1]. IgA vasculitis is the most common form of vasculitis in children, while its incidence in adults is estimated to be between 0.8 and 2.2 cases per 100,000[68]. Its severity and outcomes are worse in adults and this correlates with increased age[69]. Common clinical manifestations include palpable purpura, evidence of inflammatory arthritis, renal disease, and abdominal pain. GI involvement occurs in up to 50% of patients[70], and along with renal involvement, it is the major cause of morbidity and mortality[71,72]. Abdominal pain is described as postprandial, colicky, and periumbilical pain[70]. GI manifestations may vary from GI bleeding secondary to mucosal and submucosal vasculitis to hepatobiliary involvement. It is estimated that 3% to 5% of patients may develop bowel wall edema, necrosis, perforations, or intussusception[73]. Most of these GI manifestations tend to be self-limited[69,74] and their recurrence is more common in those with associated renal involvement[75].

In cases where treatment is warranted, glucocorticoids should be used as a first-line treatment option. In severe cases and in those who did not respond well to glucocorticoids, rituximab infusions or oral mycophenolate mofetil may help achieve remission[76,77]. Patients with intussusception, bowel perforation or severe bleeding may require surgical intervention.

CRYOGLOBULINEMIC VASCULITIS

Cryoglobulinemic vasculitis is another example of immune-complex mediated vasculitis primarily affecting small and medium-sized blood vessels[78]. Cryoglobulinemic vasculitis is usually secondary to other diseases. Brouet et al classified cryoglobulins into three categories, type I, II, and III, depending on the presence of monoclonal *vs.* polyclonal immunoglobulins[79]. In mixed forms of cryoglobulinemic vasculitis (types II and III), both IgM and IgG components can be identified along with components of the complement system. In type I, deposition of the monoclonal immunoglobulin (most commonly IgM) is seen[80]. Common clinical manifestations include the presence of various cutaneous lesions, i.e., purpura, ulcerations, sensorimotor polyneuropathy, arthralgias, and renal involvement. GI involvement is very rare, but when it happens, it is associated with poor prognosis[81]. GI involvement ranges from mesenteric vasculitis, duodenal involvement, and pancreatitis to chronic liver disease[81]. Hepatitis C virus infection remains the major cause of mixed cryoglobulinemia. Up to 50% of patients with Hepatitis C infection may have circulating cryoglobulins, but vasculitis develops only in 5% to 10% of these patients[82]. In patients with cryoglobulinemic vasculitis secondary to the hepatitis C infection, up to 60% may have liver involvement and 25% show progression to cirrhosis[83].

Diagnostic work-up in patients with suspected cryoglobulinemic vasculitis includes evaluation for underlying infections, autoimmune disease, or malignancy. Blood tests should include determination of cryoglobulins and, when present, their composition and monoclonality. Markers of inflammation, renal function, and urine microscopy with protein quantification should always be checked. Low complement levels (C3 and/or C4) and elevated rheumatoid factors are frequently found. Skin and/or renal biopsy results can help confirm the diagnosis. Treatment depends on the underlying cause and severity of disease. In many instances, the management of cryoglobulinemic vasculitis requires a multidisciplinary approach by rheumatologist, hepatologist, nephrologist, and hematologist. The goal is to suppress circulating immune complex-mediated tissue damage and to adequately treat the underlying cause. In patients with severe manifestations such as mesenteric vasculitis, treatment with high-dose corticosteroids and plasmapheresis is the first-line treatment option. To reduce risk of recurrence, rituximab or cyclophosphamide should be considered[84,85]. In those with cryoglobulinemic vasculitis associated with hepatitis C infection, antivirals are recommended as part of the treatment plan. Rituximab, in combination with antiviral therapy, was found to provide better disease outcomes compared to antiviral treatment alone[86]. Of clinical significance, treatment with IVIG may be contraindicated in cryoglobulinemic vasculitis as it may lead to precipitation of immune complex resulting in devastating multiorgan failure[87].

VARIABLE VESSEL VASCULITIS: BEHCET'S SYNDROME

Behcet's syndrome is a systemic inflammatory disease that can be complicated with vasculitis affecting blood vessels of any size or type (arteries, veins, and capillaries)[88]. There are no available diagnostic tests and diagnosis of Behcet's syndrome is based on revised international criteria for Adamantiades-Behcet's disease[89]. Typical clinical manifestations include recurrent oral and genital ulcerations, eye lesions (anterior or posterior uveitis or retinal vasculitis), skin lesions (erythema nodosum-like lesions, pyoderma gangrenosum-like lesions, papulopustular lesions, or pseudo-folliculitis), vascular involvement (arterial thrombosis, large vein thrombosis, aneurysms), and positive pathergy test[89,90].

Two types of gastrointestinal involvement have been described: Intestinal ischemia and infarction secondary to large vessel vasculitis and mucosal ulcers from neutrophilic infiltrates that can mimic IBD[91]. Behcet's syndrome can affect any segment of the gastrointestinal tract, with ileocecal involvement being the most common. In one study from Korea, 94 patients with intestinal Behcet's syndrome were included. Interestingly, 96% of them showed involvement of the terminal ileum, ileocecal valve, or cecum. Deep ulcers were more common than superficial (68% *vs.* 38%)[92]. Significant rectal involvement in Behcet's is considered to be extremely rare (< 1%)[93].

Diagnosis of Behcet's remains challenging, and in many cases, it is difficult to distinguish Crohn's disease from Behcet's syndrome as both diseases may present with extraintestinal manifestations that can overlap and both have chronic waxing and waning course. There is no standardized treatment for gastrointestinal Behcet's disease. The Japanese inflammatory bowel disease research group proposed a set of standardized treatment options, including treatments like those recommended for systemic Behcet's disease, such as colchicine, 5-ASA/Sulfasalazine, corticosteroids, immunomodulators, immunosuppressants, and TNF-a inhibitors[94]. Like in patients with IBD, surgical interventions are indicated in those patients who develop bowel perforation, fistula formation, intestinal obstruction, GI bleeding, or abdominal mass, as well as for those who are refractory to medical therapy[95]. As for GI vascular involvement such as arterial aneurysms, an endovascular approach or surgical repair continues to be the preferred method. For those with hepatic vein or IVC thrombosis, medical treatment with cyclophosphamide and corticosteroids has been recommended[96]. The use of anticoagulants remains highly controversial[96].

VASCULITIS MIMICS: NON-INFLAMMATORY VASCULAR CHANGES

Table 2 shows the spectrum of vasculitis mimics. The most common will be discussed below.

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a prominent vasculitis mimic, which is often difficult to distinguish from vasculitides. FMD is a non-atherosclerotic and non-inflammatory disease primarily seen in females[97]. FMD can affect any arterial segment, leading to arterial aneurysms, dissections, occlusions, or stenosis[98]. FMD has a predilection for renal (75% to 80%) and cranio-cervical arteries (75%)[99]. Up to two-thirds of cases may have multiple arterial involvement[100]. The exact prevalence of FMD remains unknown. A prevalence of 5.8% of renal FMD was observed among older hypertensive patients[101]. Autopsy results from the Mayo Clinic reported a 1.1% prevalence of renal FMD. Cerebrovascular FMD has a much lower prevalence, with some studies suggesting 0.1%. FMD of the visceral arteries and extremities has been rarely reported. Since radial artery access has become more commonly used for percutaneous coronary intervention, FMD is now more commonly identified in radial, brachial, and ulnar arteries[102].

In the past, FMD was classified based on which layer of the blood vessel was predominantly affected (intima, media, or adventitia)[102], but given that the percutaneous endovascular approach is currently preferred to surgery, FMD is now diagnosed radiographically. Angiographic classification recognizes two subtypes: multifocal FMD and focal FMD. The angiographic appearance of a "string of beads" correlates with the more common form of multifocal FMD, while the appearance of "circumferential or tubular stenosis" is pathognomonic of focal FMD[103]. Multifocal FMD corresponds to fibroplasia of the medial layer which accounts for more than 80% of fibromuscular lesions[104].

Disease presentation varies widely and depends on which arterial segment is primarily affected. While renal artery FMD is the most common involvement overall, with hypertension being the most common clinical manifestation, FMD can also affect the gastrointestinal tract, manifesting as "intestinal angina" or chronic

Table 2. Vasculitis mimics and clinical characteristics

Vasculitis mimics	Clinical characteristics
Vascular Ehlers-Danlos type 4 disease	Translucent skin, easy bruising, varicosities, micrognathia
IgG4-related disease	Salivary gland and lymph node enlargement, pancreatic failure, retroperitoneal fibrosis, aortitis, renal insufficiency
Fibromuscular dysplasia	Intermittent claudication, postprandial abdominal pain, weight loss, hypertension
Median arcuate ligament syndrome	Nausea, vomiting, abdominal pain, and weight loss
Erdheim-Chester disease	Xanthelasma, diabetes insipidus, exophthalmos, bone pain, ataxia
Marfan's syndrome	Disproportionately long arms, legs and fingers, scoliosis, high arched palate, aortic aneurysm, mitral valve prolapse, myopia
Thromboembolic disorders	Such as protein C or S deficiency, factor Leiden deficiency, homocystinemia. Manifestations include recurrent deep venous thrombosis, pulmonary embolisms, abdominal venous thrombosis
Antiphospholipid syndrome	Recurrent venous and arterial thrombosis, repeated miscarriages or still birth, livedo reticularis, migraine headaches, strokes, low platelets
Thromboangiitis obliterans	Smoker with recurrent episodes of thrombophlebitis, claudication, and gangrene of extremities
Infections (HIV, Syphilis, COVID-19)	Wide range of symptoms from asymptomatic to respiratory distress, clinical viral syndromes with fever, lymph adenopathy, skin rash, malaise, *etc.*
Loeys-Dietz syndrome	Blue sclera, craniosynostosis, cleft palate, hypertelorism, arterial aneurysms and dissections
Neurofibromatosis type 1	Café au lait macules, macrocephaly, short stature, neurofibromas, scoliosis, hypertension
Segmental arterial mediolysis	Nausea, vomiting, weight loss, abdominal pain, gastrointestinal hemorrhage
Cholesterol embolization syndrome	Fever, malaise, renal insufficiency, livedo reticularis, blue toe syndrome, stroke, gastrointestinal bleeding, or perforation
Neoplasms large cell B lymphoma and cardiac myxoma	Fever, malaise, lymphadenopathy, venous and arterial thrombosis, weight loss

mesenteric ischemia. These patients present with the classic triad of postprandial abdominal pain, weight loss, and epigastric bruit. Progression of vascular changes can lead to acute intestinal ischemia[105].

Vascular imaging is the primary modality of diagnosing FMD. CTA and MRA have comparable sensitivity and specificity. Conventional arteriography remains the gold standard, given that it can also measure the pressure gradient across the stenotic lesion. If a pressure gradient is more than 10%, it is considered to be hemodynamically significant stenosis. Unfortunately, it may be difficult to distinguish FMD from vasculitis given similar angiographic appearance. Clinical awareness of the two entities is important to establish a correct diagnosis. Both vasculitis and FMD can present with multisystem involvement, but given that FMD is a non-inflammatory process, patients with FMD would lack features otherwise suggestive of systemic inflammation, i.e., associated anemia, thrombocytosis, or elevated inflammatory markers. Another important layer of distinction is that vasculitis is well-known to be a progressive disease in the absence of appropriate targeted therapy, while multifocal FMD, the more common entity, is a non-progressive disease. Kadian-Dodov *et al.* identified 146 patients with multifocal carotid artery FMD who were followed with serial duplex ultrasound over a mean period of 35 months without findings of any new arterial bed development[106].

Median arcuate ligament syndrome

Median arcuate ligament syndrome (MALS) is a condition in which the median arcuate ligament compresses the celiac artery and celiac plexus. This in turn decreases the blood supply to the gut and liver. MALS may resemble multiple other abdominal disorders. The most common symptom is postprandial abdominal pain that mimics chronic mesenteric ischemia. With the increased use of CT for assessment of abdominal pain, MALS has been increasingly diagnosed. The challenge is that MALS can be an incidental finding on imaging and can coexist with other abdominal pathologies. Heo *et al.* noticed that 87% of patients with MALS had no symptoms at the time this condition was incidentally diagnosed[107]. CTA, MRA,

and duplex abdominal ultrasound during inspiration and deep expiration are the most common diagnostic tests utilized. Surgery should be reserved only for those who are symptomatic and who would therefore benefit from the laparoscopic release of the arcuate ligament. Cienfuegos *et al*. made recommendations for laparoscopic release of the arcuate ligament in young women with intense postprandial abdominal pain, and with more than 70% stenosis of the trunk or development of collateral circulation[108].

Vascular Ehlers's Danlos syndrome

Vascular Ehlers's Danlos syndrome (vEDS) is an inheritable connective tissue disorder caused by mutations of the COL3A1 gene causing defective variants of collagen type III. With the reduced amount of mature type III collagen comes the loss of mechanical strength of arteries and hollow organs, i.e., bowels and uterus[109]. Arterial dissections, aneurysms, and ruptures are the most common vascular complications, followed by GI perforations[109,110]. El Masri *et al*. analyzed 31 patients and showed that life-threatening GI complications were more likely to be seen in vEDS. Spontaneous GI perforations were the most common complication[111].

Vascular involvement may present with ectasia, aneurysm formation, dissections, or vessel occlusions that can affect any medium or large artery anywhere in the body. Patients are at risk of developing parenchymal infarcts (kidney, spleen), spontaneous vascular ruptures, or hemorrhagic events associated with interventional or surgical procedures. Diagnosis of vEDS is important, given that once arterial aneurysm is diagnosed in patients with vEDS, invasive procedures such as angiography and percutaneous interventions should be avoided due to the higher risk of arterial tear or dissection secondary to catheter-related trauma[112,113]. Therefore, noninvasive imaging such as MRA or CTA is preferred.

Patients with vEDS have subtle and variable phenotypic features compared to more classic forms of EDS. Thus, patients are frequently not aware of their condition at the time of their first vascular event. This poses another challenge to early diagnosis and thus requires better awareness of this condition by vascular surgeons, radiologists and rheumatologists. It has been proposed that vEDS should always be suspected in young patients presenting with unusual or extensive vascular involvement.

CONCLUSIONS

In this article, we describe various forms of GI involvement in patients with vasculitides or their mimics. Systemic vasculitides can cause a wide array of GI manifestations ranging from postprandial abdominal pains to lethal bowel ischemia and perforations. GI tract vasculitis can further cause erosions and ulcerations, leading to acute GI bleeding. Vascular imaging can demonstrate aneurysm formation or vessel occlusion. Both isolated GI vasculitis and systemic vasculitides can affect any blood vessel within the GI tract, most commonly mesenteric, hepatic, or splenic vessels. Ischemic infarctions of solid organs such as pancreas, liver, or gallbladder have also been well documented. Since, in many instances, symptoms are nonspecific and the spectrum of GI manifestations in systemic vasculitides is broad, correct diagnosis relies greatly on a thorough history and physical exam, along with the most appropriate choice of imaging modality. Diagnostic and therapeutic delays can be detrimental. Treatment of GI involvement depends on the underlying type of vasculitis and usually involves the use of high-dose glucocorticoids and immunosuppressive therapy. Close collaboration between surgeons, rheumatologists, radiologists, and GI specialists is crucial for optimal care. Re-evaluation is highly recommended as an initial presentation involving only one organ system can evolve over time into a full-blown multisystemic disease.

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